Remarks

Restriction Requirement

On January 31, 2003, the Examiner called Applicants with a second restriction requirement, requiring a second election into either of Group I (claims 10-23 and 30-41, bicyclic core structures) or II (claims 10-14 and 30-31, R1, R3 or R4 and R4 may form a ring). Applicants provisionally elected, with traverse, compounds falling into Group 1 (*e.g.*, bicyclic core structures, where R1 +R3 and R4 +R5 do not form a ring). Applicants hereby affirm that election. Claims 10-23 and 30-41 have been amended to read on elected Group I. The species (Example 10) elected in the first restriction requirement falls within Group I.

According to MPEP 803.02, Applicants understand that the above election is a provisional election for purposes of search and examination, and that, if the elected species is found to be allowable, Applicants' claims covering other disclosed species will be fully considered and examined.

Thus it is not understand why the Examiner only searched the elected species (example 10) in which R1 is a substituted aryl (not alkyl), and then proceeded to search only subgenerics in which R1 is alkyl. Applicants believe that since the elected species was found allowable, according to MPEP 803.02 the Examiner is obliged to search all other disclosed species within the elected Group. Applicants respectfully request that the Examiner fully search other disclosed species within elected Group 1.

It is believed the Examiner may not elect their own subgeneric once the species is found allowable, and that a final rejection based on an incomplete search would be improper.

New Matter

Applicants believe that no new matter has been added to the claims, nor have the claims been broadened by the amendments requested herein.

Rejection under 35 U.S.C. 102(b)

Claim 10 is rejected under 35 U.S.C. 102(b) as being anticipated by Yu et al., Chem Abstract 72:31563. Applicants have amended Claim 10 so that R2 cannot be hydroxy as required in the Yu compound. Accordingly, presently amended Claim 10 is not anticipated by Yu.

Rejections under 35 U.S.C. 112

Claims 10-23 and 15-41 were rejected for lack of enablement as the Examiner contends that the Specification does not enable the preparation and use of compounds wherein R2 is other than monocyclic heteroaryl or cyano.

In response, Applicants have amended Claim 10 to limit the R2 substituent to cyano or a substituted or unsubstituted monocyclic heterocyclic group. Basis for this amendment is found throughout the Examples and Claim 2 as originally filed. Claim 11 has been cancelled as being redundant. Accordingly, it is believed the Examiner's rejection for lack of enablement is moot.

The Examiner also rejected the claims for lack of enablement as "there are no working examples of experimental data to demonstrate that the compounds may inhibit IMPDH." The Examiner further contends that there is no direction or guidance for how to use the disclosed (and claimed) compounds because there is no data showing the use of Applicants' compounds nor data demonstrating the use of the compounds in combination with phosphodiesterase Type 4 inhibitors, nor data permitting the determination of an effective amount and states that the claimed uses would require undue experimentation to implement. The Examiner particularly objects to the use of the claimed compounds as preventatives. Applicants respectfully traverse.

The assay used to determine the extent of the inhibition of IMPDH is described in the Specification, pg 96, first and second paragraph. As stated therein, the compounds of the present invention inhibit the enzyme IMPDH (both I and II) at measurable levels as indicated by the aforementioned assay or by any assay which can determine an effect of inhibition of the enzyme IMPDH.

As discussed in the background of the present Specification, it is accepted that inhibitors of IMPDH I and II (e.g. "MPA") are useful immunosuppressants in the treatment of IMPDH related disorders such as transplant rejection, autoimmune disorders, psioriasis, inflammatory diseases, including rheumatoid arthritis, tumors and for the treatment of allograft rejection. See U.S. Pat. Nos 4,686,234, 4,725,622, 4,727,069, etc. (Specification, page 3). Moreover, as is also discussed in the Specification, it is recognized in the art, particularly with respect to the prevention of allograft rejections, that combinations of an IMPDH inhibitor (e.g. MPA) and cyclic AMP agonists (such as Rolipram) are useful for the prevention and/or treatment of IMPDH-associated disorders. *Id.* Accordingly, one of skill in the art reasonably expects compounds of the present invention, and combinations thereof, particularly combinations with AMP agonists, to have utility in treating and preventing IMPDH-associated disorders.

In conclusion, based on what is already known about IMPDH inhibitors, one of skill in the use of IMPDH inhibitors could use the compounds of the present invention to treat IMPDH related disorders without undue experimentation.

The Examiner has also rejected the claims for lack of enablement based on the scope of the term "prodrug", apparently because Applicants provide no guidance as how their compounds are made more active in vivo. While Applicants do not agree, in order to expedite the prosecution of this application, Applicants have amended the claims to delete the term "prodrug". The claims have also been amended to delete the term "isomers", as it is a typographical error.

Claims 10-15 and 37 have been rejected as being indefinite as the Examiner contends that it is unclear as to what the nature and number of substituent(s) is intended by "substituted" alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocycloalkyl, etc. throughout Claim 10. Applicants respectfully traverse.

According to M.P.E.P. 2173.02, "the essential inquiry pertaining to this [definiteness] requirement is whether the claims set out and circumscribe a particular subject matter with a reasonable degree of clarity and particularity. In reviewing a claim for compliance with 35 U.S.C. 112, second paragraph, the examiner must consider the claim as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope and, therefore, serves the notice function required by 35 U.S.C. 112, second paragraph. See, e.g., Solomon v. Kimberly-Clark Corp., 216 F.3d 1372, 1379, 55 USPQ2d 1279, 1283 (Fed. Cir. 2000).

Applicants have specifically defined each of the above substituents in the Specification, lines 62-70. For example, as defined on page 63 of the Specification, "alkenyl" groups are "straight or branched chain hydrocarbon groups having 2 to 12 carbon atoms and one, two or three double bonds, preferably 2 to 6 carbon atoms and one double bond". Since the definition of the substituent terms presented in the claims are well defined in the specification, they provide appropriate notification to one of skill in chemistry as to the scope of the claims. Accordingly, Applicants respectfully request withdrawal of the indefiniteness rejection.

The Examiner notes that Claim 36 improperly contains the trademark/trade name of rolipram. In response, Applicants have cancelled claim 36.

Finally, the Examiner contends that the use of "heterocycloalkyl" in the definition of R is unclear as to the array of heteroatoms as well as nature of atoms as ring members. The Examiner refers Applicants generally to In re Wiggins 179 USPQ 421 for certain terminology regarding heterocyclic ring systems, but provides no explanation as to why he considers the term "heterocycloalkyl" indefinite. Since there is no apparent R group in the claims, Applicants assume that this rejection is to be applied to any use of "heterocycloalkyl" in the claims. Applicants respectfully traverse.

In the Specification, page 66, the term "heterocycloalkyl" is specifically defined as "substituted and unsubstituted saturated or partially saturated monocyclic rings of 3 to 7 members and bicyclic rings of 7 to 11. The Examiner appears to object to the description of the array and nature of the heteroatoms. However, the atoms are specifically described in the specification. As stated in the Specification, page 66, each ring may have one or two O or S atoms and/or one to four N atoms provided that the total number of heteroatoms is four or less and that the heterocycloalkyl ring contains at least one carbon atom. Moreover, the nature of the heteroatoms is described as follows: [t]he nitrogen and sulfur atoms may optionally be oxidized, and the nitrogen atoms may optionally be quaternized. One having chemical skill readily understands the valence principles limiting the possible array of the heteroatoms in the heteroarylalkyl groups thereby not requiring explicit statement in the definition.

Accordingly, Applicants assert that the term "heterocycloalkyl" is well defined in the Specification, and that one of skill in the art is given ample notice as to the scope of the term as required by M.P.E.P. 2173.02. Accordingly withdrawal of the indefiniteness rejection is respectfully requested.

Applicants believe that each of the Examiner's grounds for rejection is properly stated, traversed, accommodated or rendered moot and that the present application is now in condition for allowance.

FEES

No fees should be due. However, if it is determined that a fee is due, please charge same to Deposit Account No. 19-3880 in the name of Bristol-Myers Squibb Company.

The Examiner is invited to contact the undersigned by telephone, at the number listed below, if it is believed that a telephonic communication would facilitate the prosecution of this application.

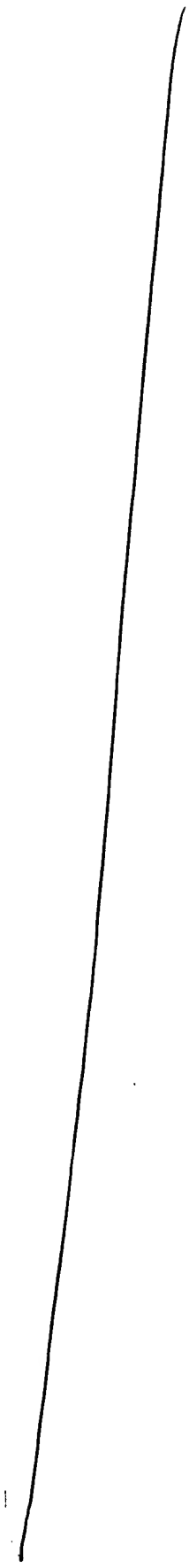
Respectfully submitted,

Bristol-Myers Squibb Company

Patent Department
P.O. Box 4000
Princeton, NJ 08543-4000
609-252-5323

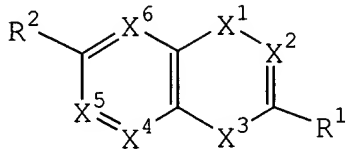
Laurelee A. Duncan.
Attorney for Applicants
Reg. No. 44,096

Date: May 5, 2003



Marked-up Version to Show Changes to the Claims

10. A compound of formula (I)



(I)

including [isomers,] enantiomers, diastereomers, tautomers, pharmaceutically acceptable salts, [prodrugs] and solvates thereof wherein:

X^1 is C=O

X^2 is CR^3;

X^3 is–NH

X^4 is CR^4;

X^5 is CR^5;

X^6 is CR^6;

R^1 is alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heterocycloalkyl, or heteroaryl;

R^2 is cyano[, hydroxy, oxo (double bond is no longer present between CR^2 and X^6), SR^7, $S(O)R^7$, SO_2R^7, $SO_2NR^8R^9$, CO_2R^7, $C(O)NR^8R^9$, or heteroaryl] <u>or a substituted or unsubstituted monocyclic heteroaryl group</u>;

R^3 is hydrogen, hydroxy, halogen, cyano, CO_2R^7, NR^8R^9, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heterocycloalkyl or heteroaryl;

R^4, R^5, and R^6 are independently selected from the group consisting of hydrogen, halogen, nitro, cyano,
O-R^7, NR^8R^9, SR^7, $S(O)R^7$, SO_2R^7, SO_3R^7, $SO_2NR^8R^9$, CO_2R^7, $C(O)NR^8R^9$, C(O)alkyl, C(O)substituted alkyl, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl and substituted alkynyl;

R^7, R^{10}, and R^{11}, are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, alkynyl, cycloalkyl, substituted cycloalkyl, C(O)alkyl, C(O)substituted alkyl, C(O)cycloalkyl, C(O) substituted cycloalkyl, C(O)aryl,

C(O)substituted aryl, C(O)Oalkyl, C(O)Osubstituted alkyl, C(O)heterocycloalkyl, C(O)heteroaryl, aryl, substituted aryl, heterocycloalkyl and heteroaryl;

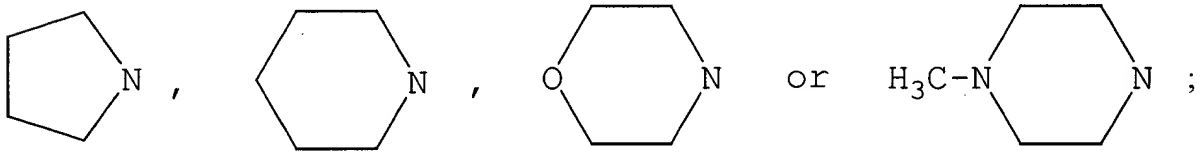
R^8 and R^9 are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, alkynyl, C(O)alkyl, C(O)substituted alkyl, C(O)cycloalkyl, C(O)substituted cycloalkyl, C(O)aryl, C(O)substituted aryl, C(O)Oalkyl, C(O)Osubstituted alkyl, C(O)heterocycloalkyl, C(O)heteroaryl, aryl, substituted aryl, heterocycloalkyl, and heteroaryl or R^8 and R^9 taken together with the nitrogen atom to which they are attached complete a heterocycloalkyl or heteroaryl ring;

R^3 and R^1 may be taken together with the carbon atoms to which they are attached to form a monocyclic or substituted monocyclic ring system of 5 or 6 carbon atoms; and

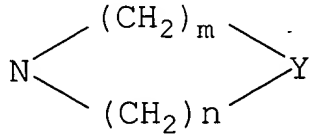
R^4 and R^5 may be joined together by the chain –O-CH_2-O- or -O-CH_2-CH_2-O-;

with the following provisos:

(a) When ~~X^1 is C=O, X^2 is CR^3, X^3 is NH, X^4 is CR^4, X^5 is CR^5, X^6 is CR^6,~~ R^1 is substituted or meta unsubstituted phenyl, R^3 is H, R^4 is H, R^5 is H and R^6 is H, then R^2 is not PhCONH,



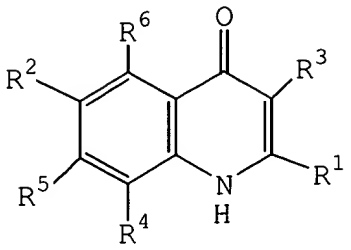
(b) when ~~X^1 is C=O, X^2 is CR^3, X^3 is NH, X^4 is CR^4, X^5 is CR^5, X^6 is CR^6,~~ R^1 is phenyl substituted with H, F, Cl, Br, I, CH_3, CF_3, OH, OCH_3, OCF_3, OCH_2CH_3, NH_2, $NHCH_3$, $N(CH_3)_2$, O-benzyl, -C(=O)-R_0, or -C(=O)-OR_0 and R_0 is a lower alkyl group, R^3 is H, R^4 is H, R^5 is H and R^6 is H, then R^2 is not



where Y is CH_2, O or S, m and n are each greater than 1, and the sum of m and n is between 3 and 6; and

(c) when R^2 is heteroaryl, at least one of the heteroatoms must be O.

12. A compound of Claim [11] 10 of formula (III)



(III)

including [isomers], enantiomers, diastereomers, tautomers, pharmaceutically acceptable salts, [prodrugs] and solvates thereof wherein:

R^2 is 4-oxazolyl, substituted 4-oxazolyl, 5-oxazolyl, or substituted 5-oxazolyl;

R^3 is hydrogen, hydroxy, NR^8R^9, alkyl of 1 to 4 carbons, alkenyl of 2 to 4 carbons, alkynyl of 2 to 4 carbons, substituted alkyl of 1 to 4 carbons, phenyl, substituted phenyl, cycloalkyl of 5 to 7 carbons, substituted cycloalkyl of 5 to 7 carbons, monocyclic heterocycloalkyl and monocyclic heteroaryl;

R^4 is hydrogen, halogen, nitro, hydroxy, alkyl of 1 to 4 carbons, cyano, CF_3, OCF_3, OCH_3, SCH_3, $S(O)CH_3$, or $S(O)_2CH_3$;

R^5 is hydrogen, halogen, nitro, hydroxy, alkyl of 1 to 4 carbons, cyano, vinyl, CF_3, CF_2CF_3, $CH=CF_2$, OCH_3, OCF_3, $OCHF_2$, SCH_3, $S(O)CH_3$, or $S(O)_2CH_3$; and

R^6 is hydrogen, halogen, nitro, hydroxy, alkyl of 1 to 4 carbons, cyano, CF_3, OCH_3, OCF_3, SCH_3, $S(O)CH_3$, and $S(O)_2CH_3$.

13. A compound of Claim 12 including [isomers,] enantiomers, diastereomers, tautomers, pharmaceutically acceptable salts, [prodrugs] and solvates wherein:

R^2 is 4-oxazolyl, substituted 4-oxazolyl, 5-oxazolyl, substituted 5-oxazolyl or heteroaryl;

R^3 is hydrogen, hydroxy, halogen, methyl or NR^8R^9;

R^4 is hydrogen;

R^5 is halogen, methyl, ethyl, substituted alkenyl, alkyne, OMe or OCF_3; and

R^6 is hydrogen.

14. A compound of Claim 13 including [isomers,] enantiomers, diastereomers, tautomers, pharmaceutically acceptable salts, [prodrugs] and solvates wherein:

R^2 is 4-oxazolyl, substituted 4-oxazolyl, 5-oxazolyl or substituted 5-oxazolyl;

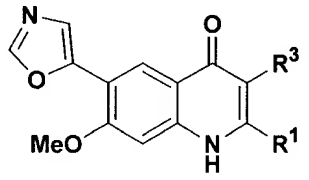
R^3 is hydrogen, hydroxy, halogen or methyl;

R^4 is hydrogen;

R^5 is halogen, methyl or OMe; and

R^6 is hydrogen.

15. A compound of Claim 10 of formula (V)

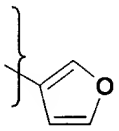


(V)

including [isomers,] enantiomers, diastereomers, tautomers, pharmaceutically acceptable salts, [prodrugs] and solvates
selected from:

a compound of formula (V) wherein:

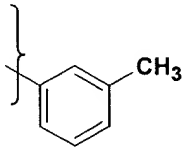
R^1 is



and R^3 is hydrogen;

a compound of formula (V) wherein:

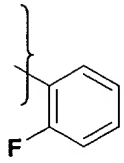
R^1 is



and R^3 is hydrogen;

a compound of formula (V) wherein:

R^1 is



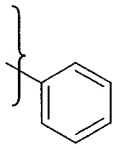
and R^3 is hydrogen;

a compound of formula (V) wherein:

R^1 is CH_3 and R^3 is hydrogen;

a compound of formula (V) wherein:

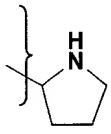
R^1 is



and R^3 is CH_3;

a compound of formula (V) wherein:

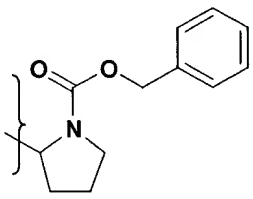
R^1 is



and R^3 is hydrogen;

a compound of formula (V) wherein:

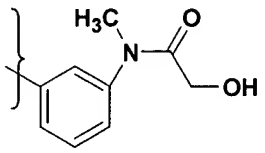
R^1 is



and R^3 is hydrogen;

a compound of formula (V) wherein:

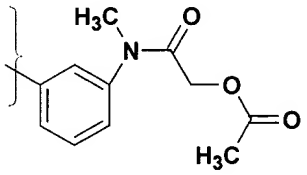
R^1 is



and R^3 is hydrogen;

a compound of formula (V) wherein:

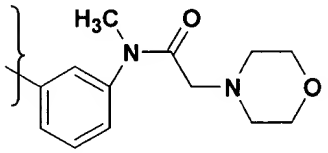
R^1 is



and R^3 is hydrogen;

a compound of formula (V) wherein:

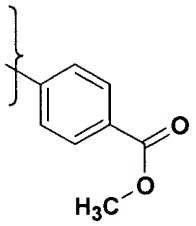
R^1 is



and R^3 is hydrogen;

a compound of formula (V) wherein:

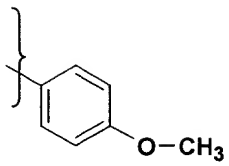
R^1 is



and R^3 is hydrogen;

a compound of formula (V) wherein:

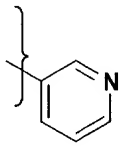
R^1 is



and R^3 is hydrogen;

a compound of formula (V) wherein:

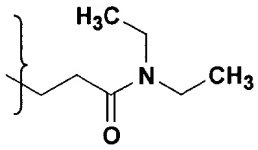
R^1 is



and R^3 is hydrogen;

a compound of formula (V) wherein:

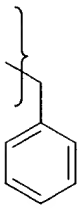
R^1 is



and R^3 is hydrogen;

a compound of formula (V) wherein:

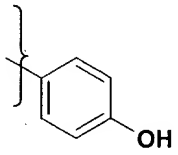
R^1 is



and R^3 is hydrogen;

a compound of formula (V) wherein:

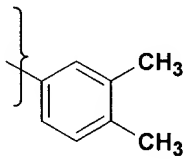
R^1 is



and R^3 is hydrogen;

a compound of formula (V) wherein:

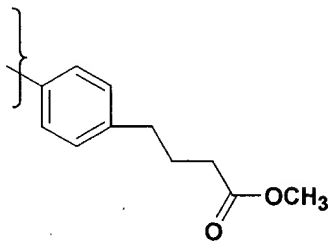
R^1 is



and R^3 is hydrogen;

a compound of formula (V) wherein:

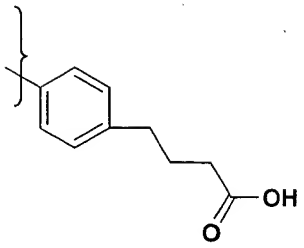
R^1 is



and R^3 is hydrogen;

a compound of formula (V) wherein:

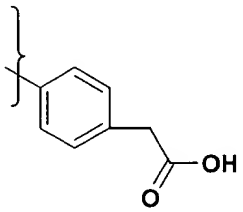
R^1 is



and R^3 is hydrogen;

a compound of formula (V) wherein:

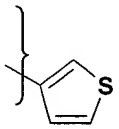
R^1 is



and R^3 is hydrogen;

a compound of formula (V) wherein:

R^1 is



and R^3 is hydrogen;

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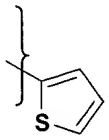

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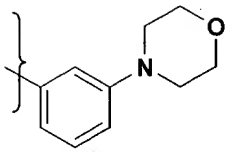

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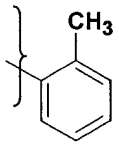

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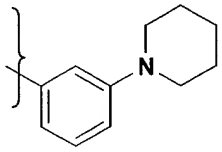

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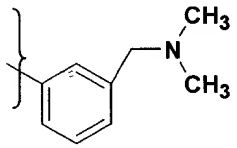

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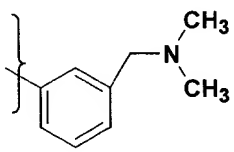

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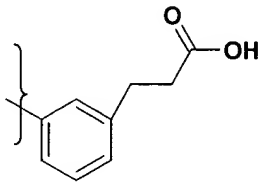

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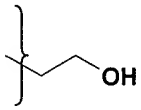

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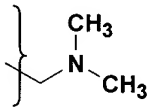

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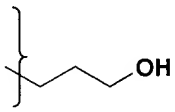

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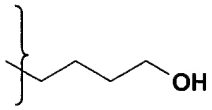

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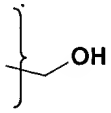

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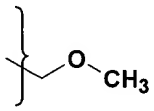

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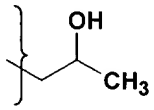

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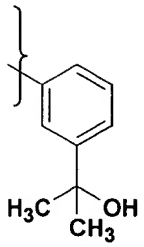

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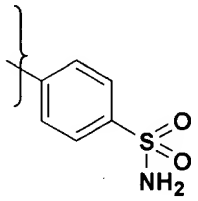

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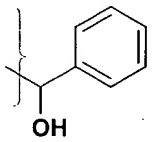

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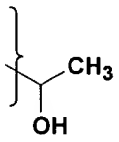

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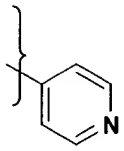

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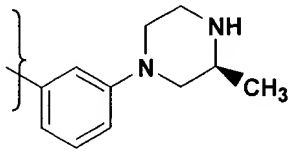

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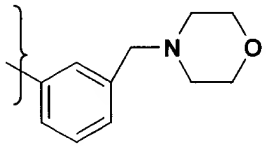

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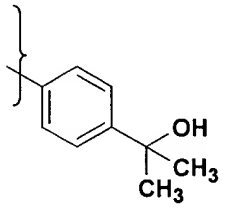

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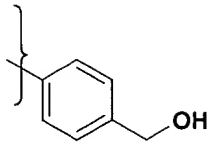

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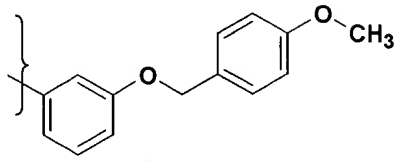

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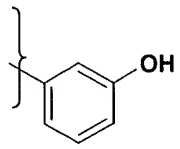

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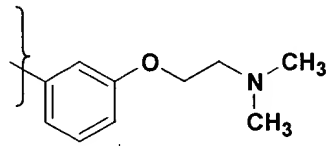

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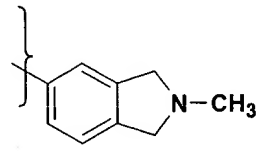

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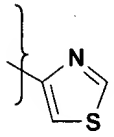

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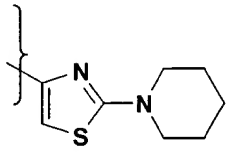

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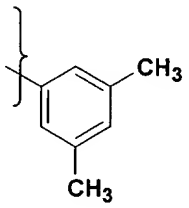

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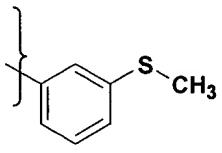

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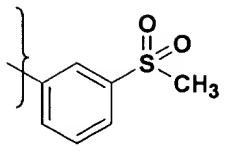

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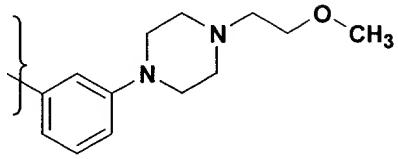

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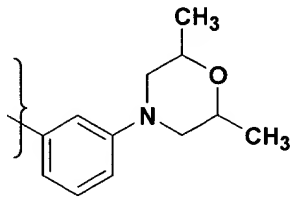

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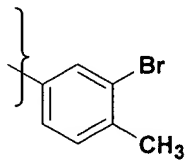

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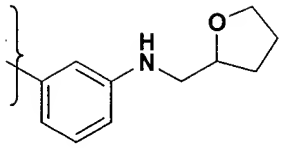

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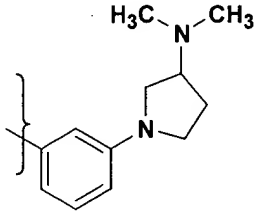

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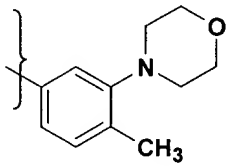

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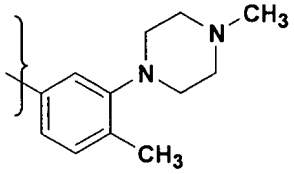

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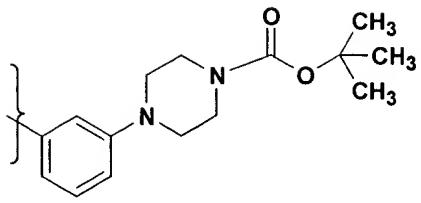

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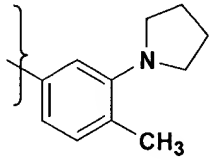

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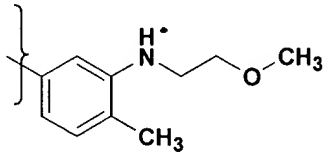

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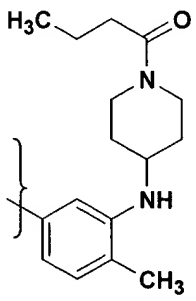

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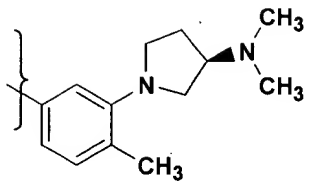

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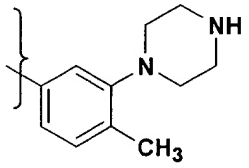

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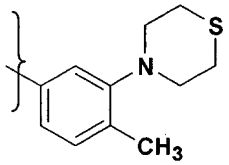

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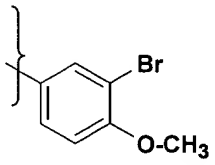

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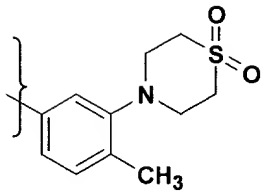

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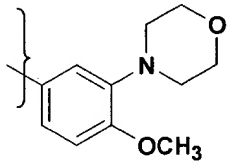

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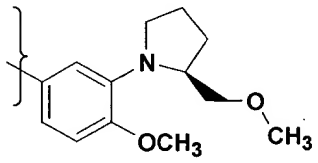

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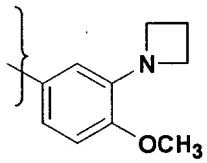
a compound of formula (V) wherein:

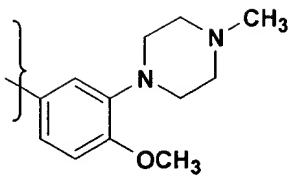
R^1 is



and R^3 is hydrogen;

a compound of formula (V) wherein:

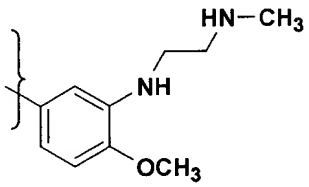
R^1 is



and R^3 is hydrogen;

a compound of formula (V) wherein:

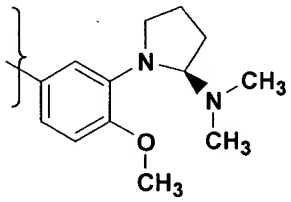
R^1 is



and R^3 is hydrogen;

a compound of formula (V) wherein:

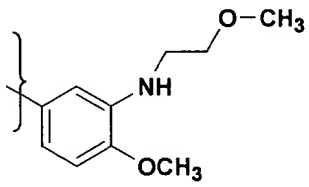
R^1 is



and R^3 is hydrogen;

a compound of formula (V) wherein:

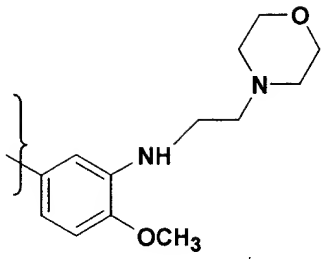
R^1 is



and R^3 is hydrogen;

a compound of formula (V) wherein:

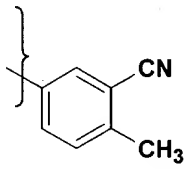
R^1 is



and R^3 is hydrogen;

a compound of formula (V) wherein:

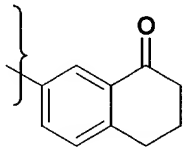
R^1 is



and R^3 is hydrogen;

a compound of formula (V) wherein:

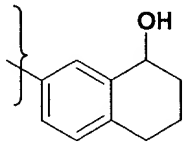
R^1 is



and R^3 is hydrogen;

a compound of formula (V) wherein:

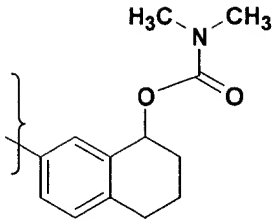
R^1 is



and R^3 is hydrogen;

a compound of formula (V) wherein:

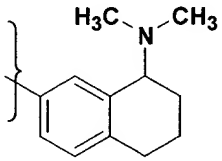
R^1 is



and R^3 is hydrogen;

a compound of formula (V) wherein:

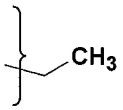
R^1 is



and R^3 is hydrogen;

a compound of formula (V) wherein:

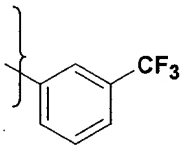
R^1 is



and R^3 is hydrogen;

a compound of formula (V) wherein:

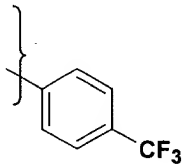
R^1 is



and R^3 is hydrogen;

a compound of formula (V) wherein:

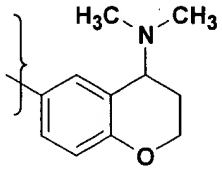
R^1 is



and R^3 is hydrogen;

a compound of formula (V) wherein:

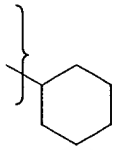
R^1 is



and R^3 is hydrogen;

a compound of formula (V) wherein:

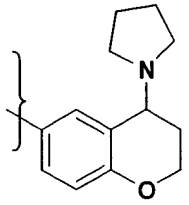
R^1 is



and R^3 is hydrogen;

a compound of formula (V) wherein:

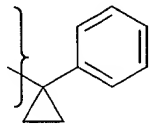
R^1 is



and R^3 is hydrogen;

a compound of formula (V) wherein:

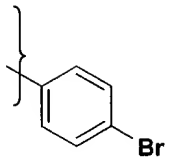
R^1 is



and R^3 is hydrogen;

a compound of formula (V) wherein:

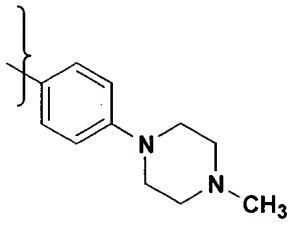
R^1 is



and R^3 is hydrogen;

a compound of formula (V) wherein:

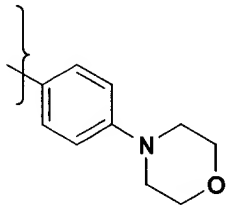
R^1 is



and R^3 is hydrogen;

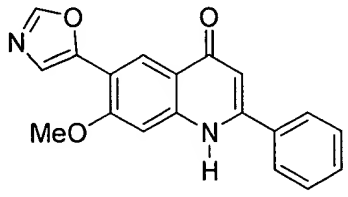
and a compound of formula (V) wherein:

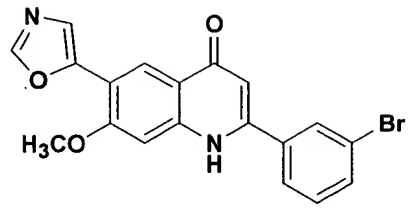
R^1 is

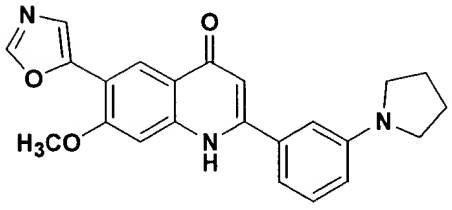


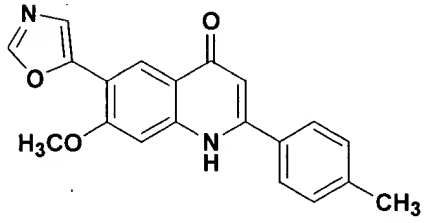
and R^3 is hydrogen.

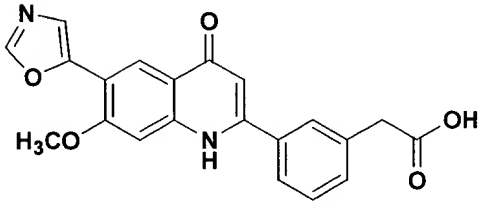
16. A compound of Claim 10 including [isomers,] enantiomers, diastereomers, tautomers, pharmaceutically acceptable salts, [prodrugs] and solvates thereof selected from:

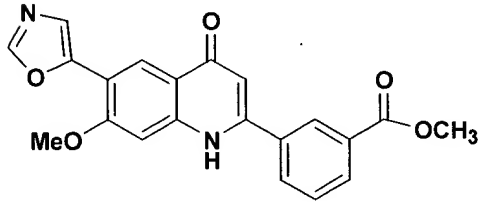


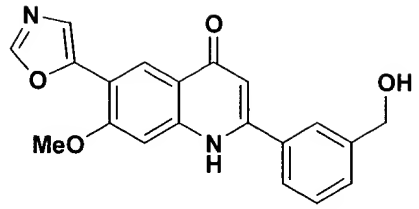


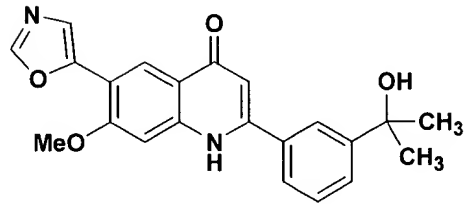


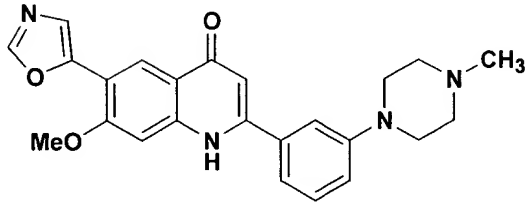


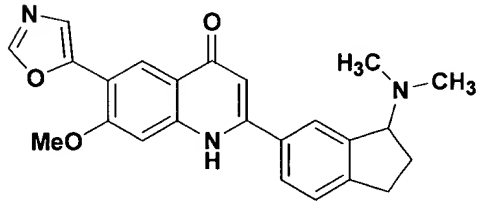


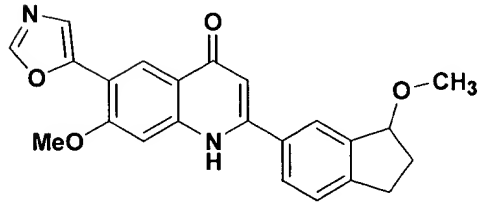


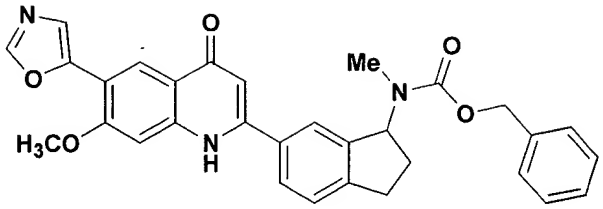


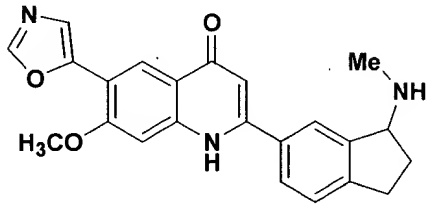


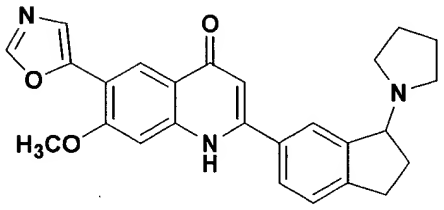


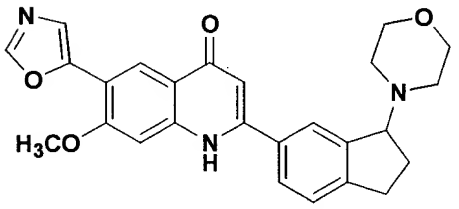


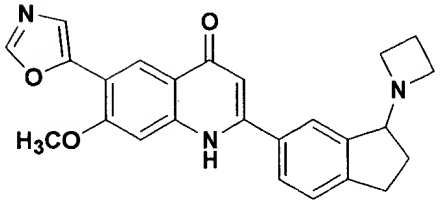


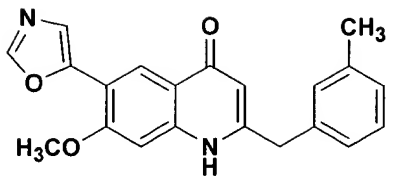


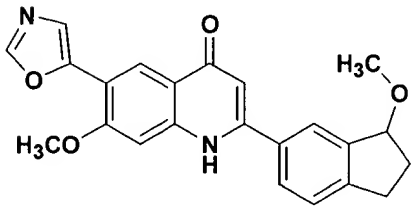


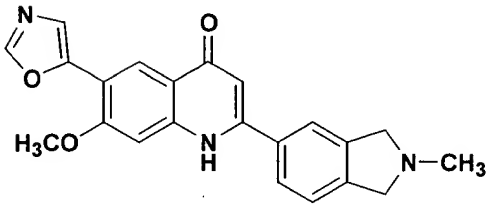


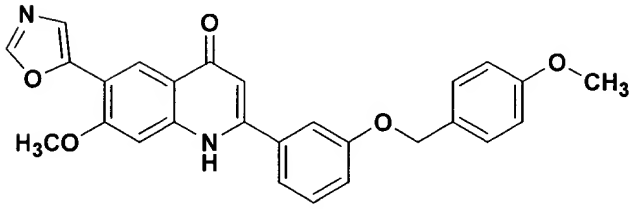


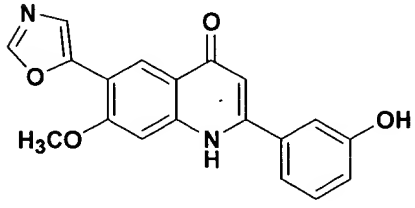


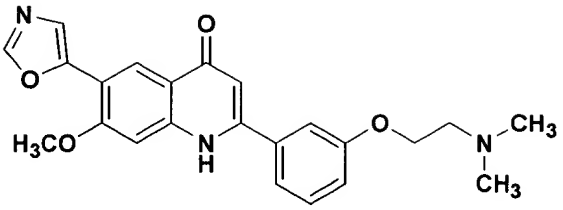


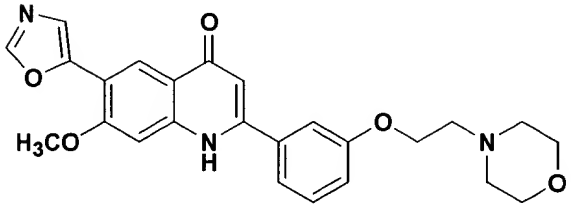


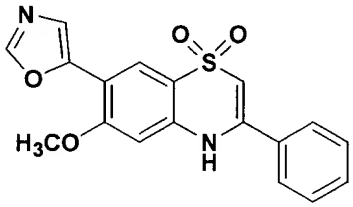


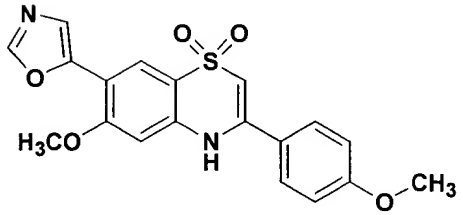


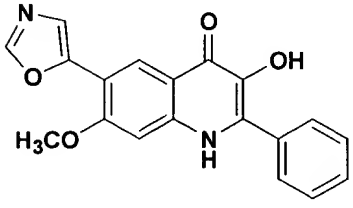


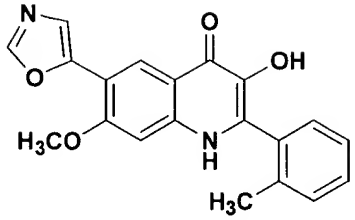


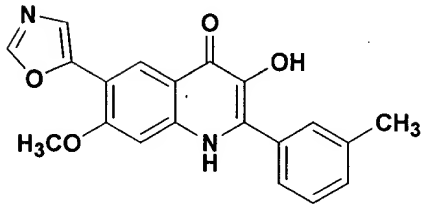


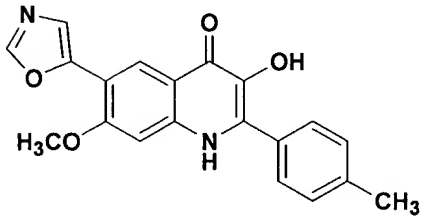


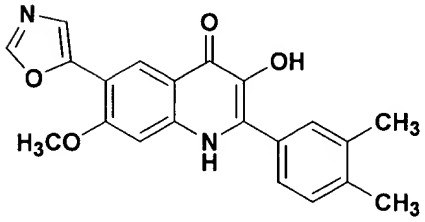


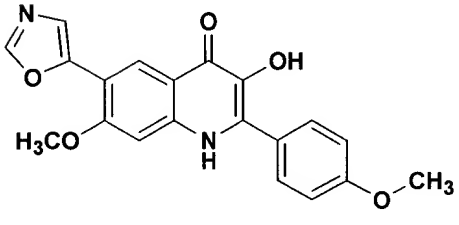


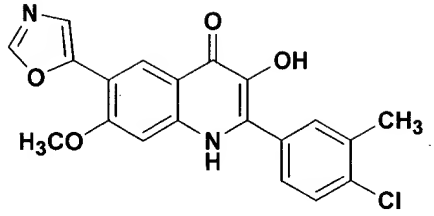


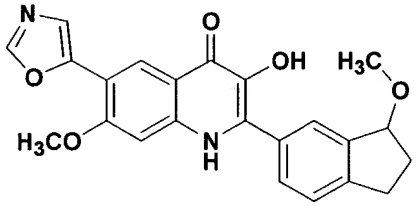


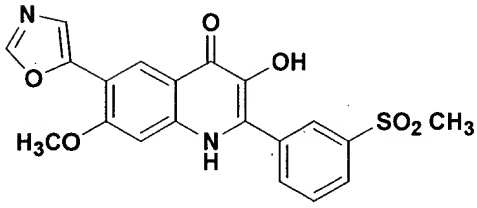


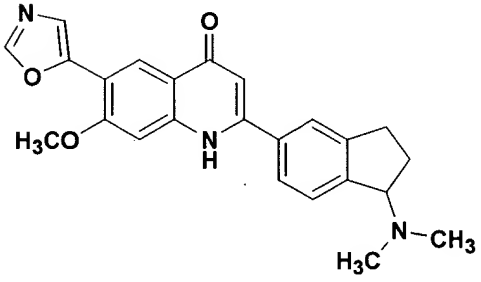


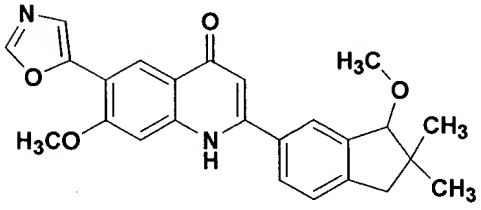


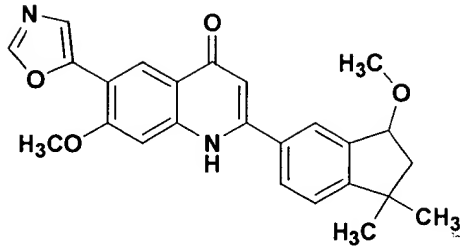


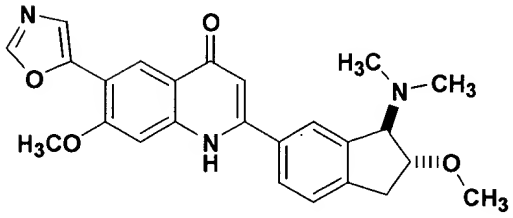


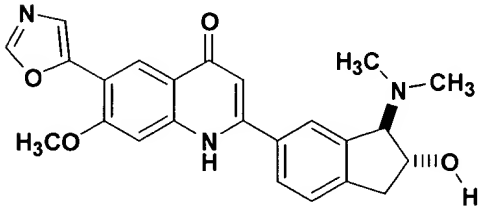


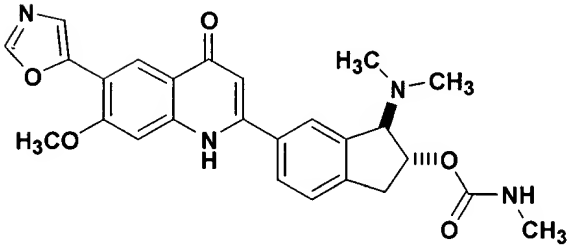


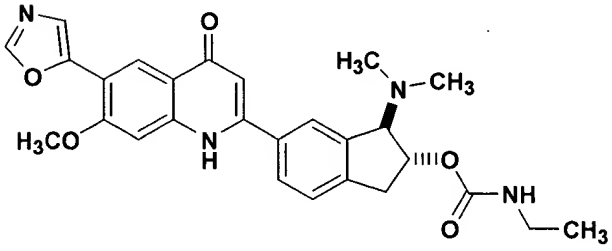


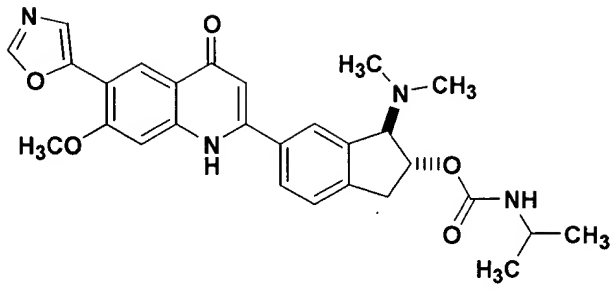


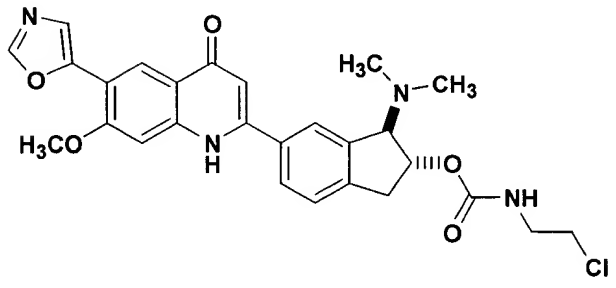


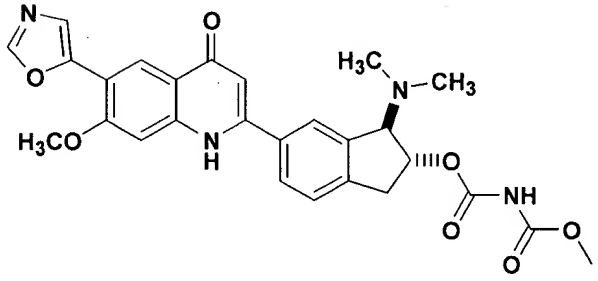


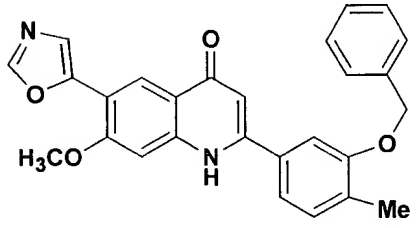


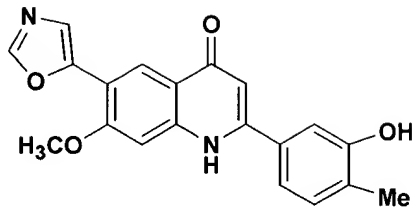


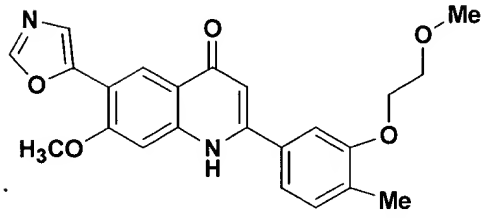


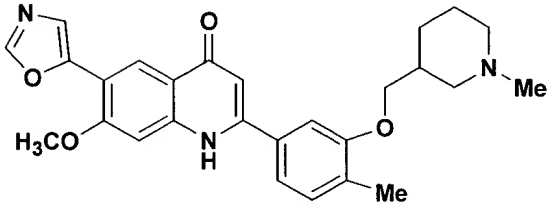


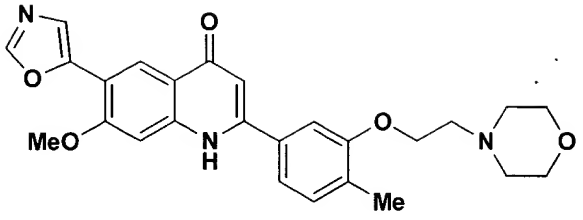


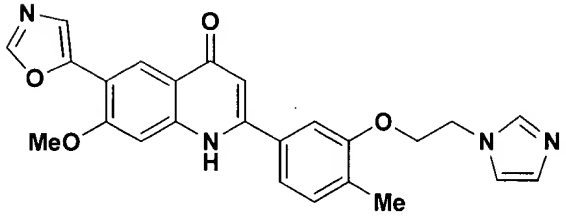


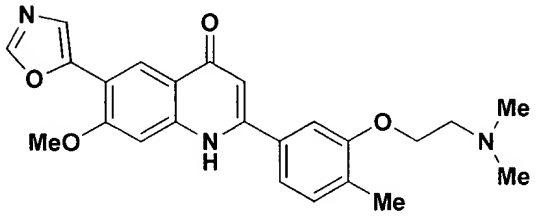


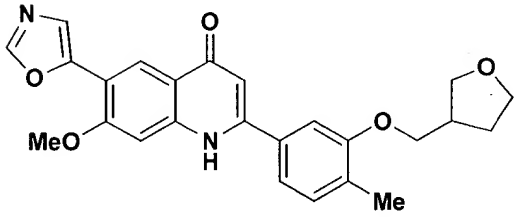


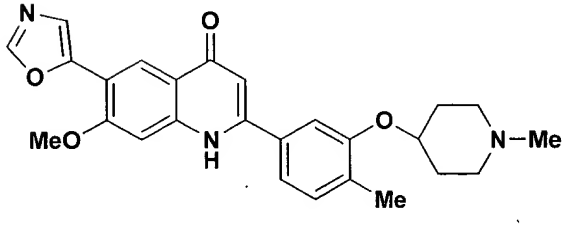


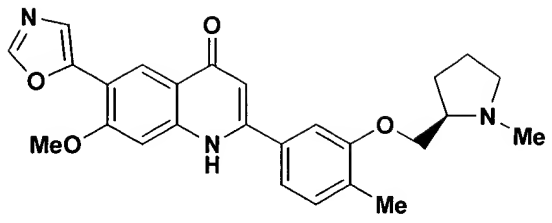


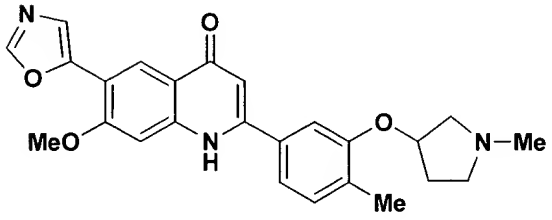


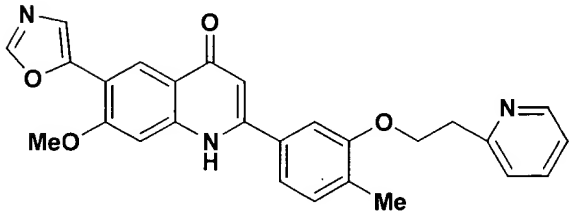


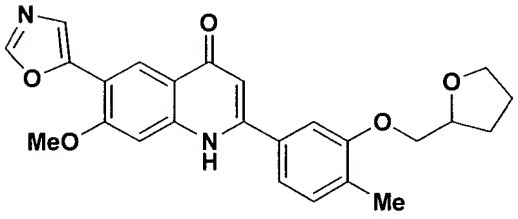


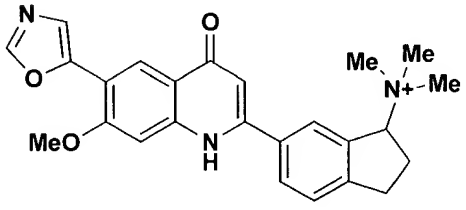


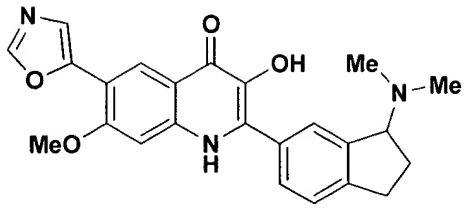


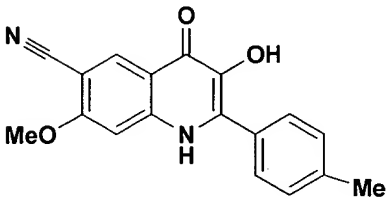


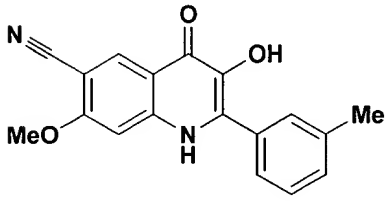


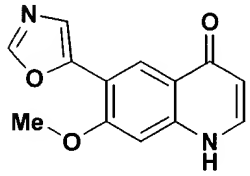


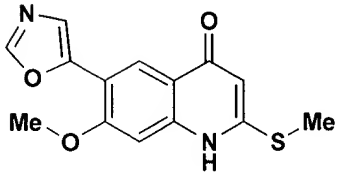


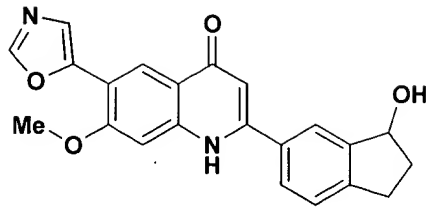


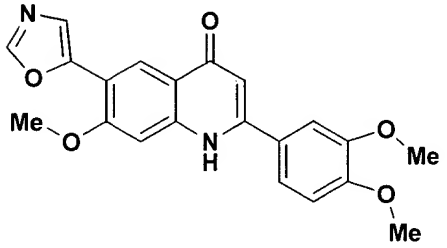


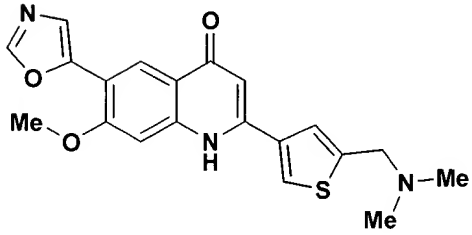


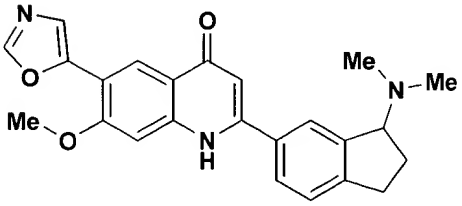


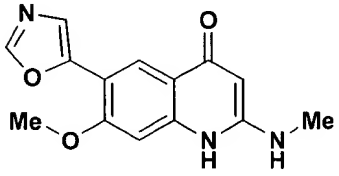


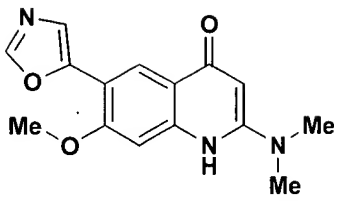


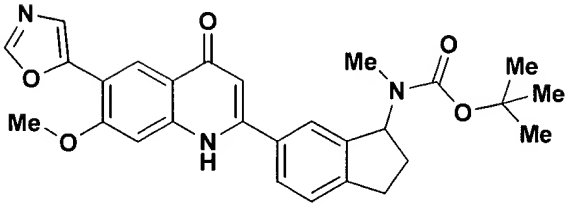


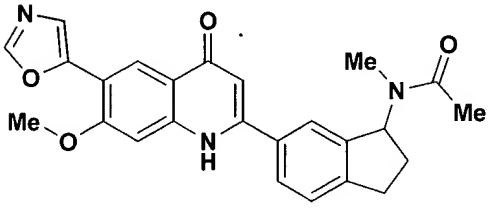


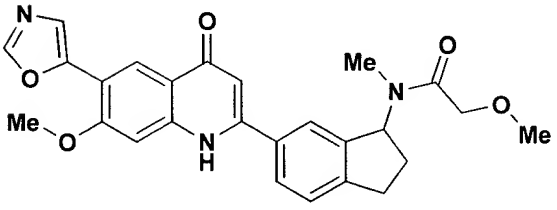


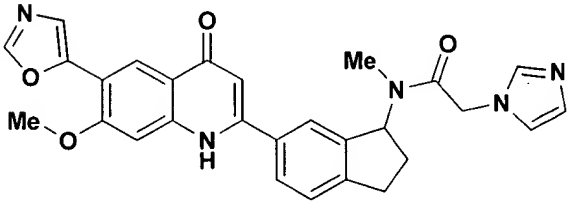


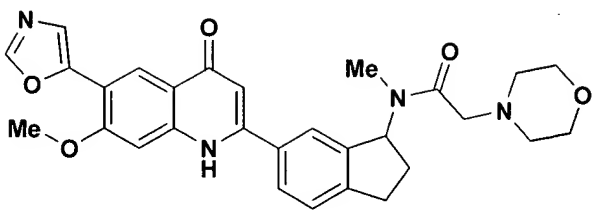


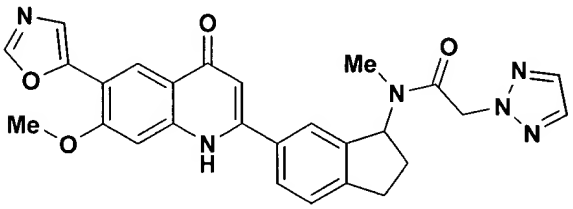


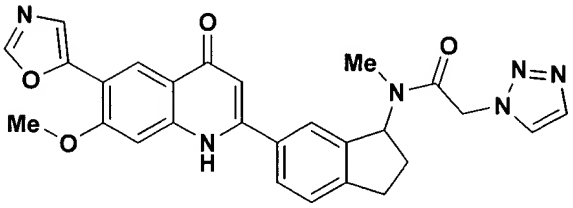


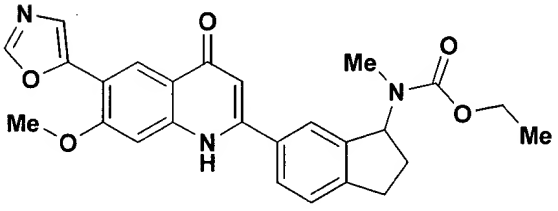


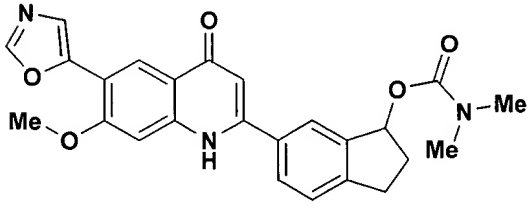


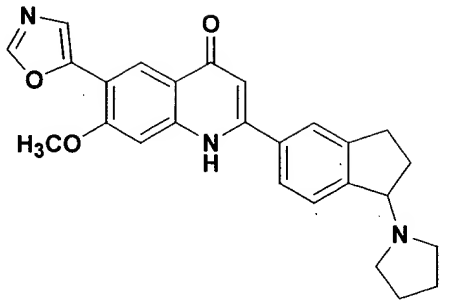


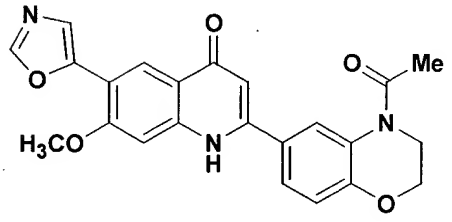


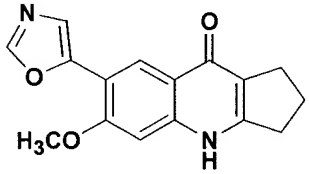












and